Paper No. 46

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GERMAIN FUH and JAMES A. WELLS

Appeal No. 1999-1732
Application No. 08/308,879

ON BRIEF

Before WINTERS, SCHEINER and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 and 3-7. Claim 1 is representative of the subject matter on appeal, and reads as follows:

1. A method for inhibiting the growth of breast cancer cells expressing prolactin receptors comprising contacting the cells with an effective amount of a growth hormone analog, wherein the analog is an antagonist which binds to the prolactin receptor and the analog is a variant of a naturally occurring growth hormone which includes an amino acid variation that reduces growth hormone receptor binding at site two by at least two-fold in relation to native growth hormone.

The examiner relies on the following references:

Kopchick et al. (Kopchick) 5,350,836 Sep. 27, 1994

Phares, "Regression of Rat Mammary Tumors Associated with Suppressed Growth Hormone," Anticancer Research, Vol. 6, pp. 845-848 (1986).

Watahiki et al. (Watahiki), "Conserved and Unique Amino Acid Residues in the Domains of the Growth Hormones," J. Biol. Chem., Vol. 264, pp. 312-316 (1989).

Chen et al. (Chen), "Expression of a mutated bovine growth hormone gene suppresses growth of transgenic mice," Proc. Natl. Acad. Sci., Vol. 87, pp. 5061-5065 (1990).

Claims 1 and 3-7, which stand or fall together, stand rejected under 35 U.S.C. § 103(a) as being obvious over Kopchick. In addition, claims 1 and 3-7 stand rejected under 35 U.S.C. § 103(a) over the combination of Chen, Phares and Watahiki. After careful review of the record before us, we reverse both rejections.

BACKGROUND

Growth hormone is a member of a homologous hormone family that also includes prolactins, placental lactogens, and other genetic and species variants of growth hormone. Human growth hormone not only binds to its own receptor, but can also bind to either cloned somatogenic or prolactin receptors. See Specification, page 3. The human growth hormone sequence is known, and the hormone has been cloned. See id. at pages 3-4.

Prolactin and growth hormone are known to play a role in the development and progression of breast cancer. The majority of breast cancer cells overexpress the prolactin

receptor, and human breast cancer cell lines have been shown to respond to both prolactin and growth hormone when grown as solid tumors in nude mice. See id. at page 5.

Growth hormone and the class of conformational ligands to which they belong form a 1:2 complex with their receptor, with a first ligand binding site, which the specification refers to as site 1, binds to a first receptor, and then a second receptor binds to the hormone at the second ligand site, site 2. See id. at page 6. Coupled with the knowledge of the conformational structure of the ligand, the specification states that one can design hormone agonists or antagonists by introducing amino acid variations into sites 1 and/or 2. See id. at pages 6-7. The specification states that

> [i]n particular, antagonists for polypeptide ligands are provided which comprise an amino acid sequence mutation in site 2 which reduces or eliminates the affinity of the ligand for the receptor at site 2. Ideally, the ligand antagonist analog will have low or no affinity for receptor at site 2 and will have elevated affinity for receptor at site 1.

Id. at page 7.

The claimed invention is drawn to a method for inhibiting growth of breast cancer cells through the use of a growth factor antagonist, wherein the antagonist has an amino acid variation that reduces ligand binding at site 2 by at least two-fold. Also claimed is a preferred antagonist, wherein the glycine at position 120 of human growth hormone has been mutated to arginine (G120R).

DISCUSSION

The answer contains two grounds of rejection, both based on obviousness. We will address the obviousness rejection in reverse order, addressing the rejection over Kopchick first.

The Answer relies on the Kopchick reference for teaching growth hormone receptor antagonists, and specifically for teaching that the mutant in which the glycine at position 120 has been mutated to arginine (G120R) is a growth receptor antagonist. With respect to the use of using such growth hormone antagonists to treat breast cancer, the Kopchick reference states:

> It has been suggested that long-activity somatostatin analogues may have value in the control of breast and prostate cancers. Manni, Biotherapy, 4:31-36 (1992). Manni hypothesizes that they could inhibit tumor growth by a number of mechanisms, including inhibiting growth hormone secretion. Growth hormone is implicated because it is lactogenic and because it elevates IGF-1 levels. We suggest that the growth hormone antagonists of the present invention may be used in the treatment of cancers whose growth is facilitated by endogenous growth hormone or IGF-1.

Kopchick, Col. 3, line 60-Col. 4, line 2 (emphasis added). The reference, however, presents no examples, nor does it provide in vitro or in vivo data, wherein the disclosed growth hormone antagonists are administered to breast cancer cells that express prolactin receptors, as required by claim 1.

Based on this single paragraph in the Kopchick reference, the Answer concludes that "it would have been obvious to a person of ordinary skill in the art to administer [growth

hormone] antagonists such as [G120R] to mammary tumor cells or patients having breast cancer to regress tumor growth because Kopchick et al. teach that [growth hormone] antagonists are useful in the treatment of breast cancer. See Answer, pages 5-6.

Appellants argue that the statements in the Kopchick reference are merely an invitation to experiment, or that it is merely obvious to try the process suggested by the reference, and thus that the reference does not provide a reasonable expectation of success of inhibiting the growth of breast cancer cells using a growth hormone antagonist. We agree.

A determination of obviousness not only requires that the prior art would have suggested the claimed process to one of ordinary skill in the art, but also that the process would have a reasonable likelihood of success when viewed in light of the prior art. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). A rejection based on a reference or a combination of references amounts to an "invitation to experiment," and is thus "obvious-to-try," "when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). The Kopchick reference, while suggesting that growth hormone antagonists may be used in the treatment of cancers whose growth is facilitated by endogenous growth

hormone, does not contain a sufficient teaching that the claimed result would be obtained. Thus, the answer fails to set forth a prima facie case that the claims are rendered obvious by the Kopchick reference.

The treatment of cancers, such as breast cancer, is an unpredictable art. The somatostatin analogues discussed by Kopchick are hypothesized to inhibit tumor growth by inhibiting growth hormone secretion. See Kopchick, col. 3, lines 63-65. But that is only one of a number of hypothesized mechanisms by which somatostatin analogues may inhibit tumor growth. Even if somatostatin analogues act to inhibit tumor growth by suppressing serum growth hormone levels, growth hormone antagonists, however, actually increase the production of endogenous growth hormone in the pituitary, and may lead to increased serum growth hormone levels. See Cronin Declaration, page 6. Therefore, the growth hormone antagonists and the somatostatin analogues work by different mechanisms, and thus the ordinary artisan would not have a reasonable expectation of success from data produced by somatostatin analogues in inhibiting breast cancer growth to translate to success with growth hormone antagonists.

The claims were also rejected as obvious over the teachings of the combined teachings of Phares, Chen and Watahiki.

The Phares reference uses a growth hormone agonist, pleroceroid growth factor (PGF) to study the effect of endogenous growth hormone levels on the growth of 7, 12, dimethylbenz(a)anthracene (DMBA)- or N-nitrosomethylurea (NMU)-induced rat mammary

tumors in vivo. Phares found that PGF caused regression of most of the mammary tumors induced by DMBA or NMU, and that endogenous growth hormone serum levels were also reduced. The Answer also relied on Phares for teaching that growth hormone has been implicated as a growth stimulant for rat mammary tumors and for human breast cancer cells, which may be due to its regulatory influence prolactin receptors. The reference also states that NMU-induced mammary tumors are regressed by the inhibition of growth hormone release from the hypothesis with somatostatin, leading to the conclusion that growth hormone plays an active role in mammary tumor formation. The Answer acknowledges that the reference does not teach the use of a growth hormone receptor antagonist to regress mammary tumor cell growth, but asserts that a "routineer would reasonably expect that the removal of [growth hormone] influence at the [prolactin] and estrogen receptors located on mammary tumor cells will cause tumor regression because decreased serum levels of [growth hormone] and, then, reduced activity at the receptors, has been shown to regress mammary tumors." Answer, pages 4-5.

The Answer characterizes Chen as teaching a bovine growth hormone antagonist, wherein three substitutions have been made. Watahiki is then relied upon for teaching the identity of growth hormones across several species, and that if the mutations had been made to human growth hormone, one of the substitutions would have been G120R.

The rejection concludes that it would have been obvious to the ordinary artisan to substitute the PGF as used by Phares to reduce growth hormone levels with the growth

hormone antagonist taught by Chen "because the antagonist would be expected to reduce [growth hormone] activity or influence at the mammary tumor cell [prolactin] and estrogen receptors like the reduced serum [growth hormone] levels found after PGF." Answer, page 5. Because Phares teaches that NMU-induced rat mammary tumors are regressed with decreased growth hormone influence, the Answer also concludes that there is a reasonable expectation of success that receptor antagonism would be useful for the treatment of breast cancer.

Appellants put forth several arguments why the combination of Phares, Chen and Watahiki do not render the claimed process of inhibiting the growth of breast cancer cells obvious. In particular, Appellants argue that at most, the combination provides an invitation to experiment, and thus does not produce a reasonable expectation of success. Again, we agree, for basically the same reasons discussed above with respect to the rejection over Kopchick.

As pointed out by Appellants, the PGF used by Phares to treat NMU-induced rat mammary tumors is a growth hormone agonist. As with the somatostatin analogues, growth hormone agonists decrease serum growth hormone levels. In contrast, as explained in the expert declaration, growth hormone antagonists may actually increase serum growth hormone levels. Moreover, the differences in mechanism between the growth hormone agonist PGF and growth hormone antagonists are also demonstrated by the fact that PGF treated animals demonstrate increased growth, whereas growth hormone

antagonist treated animals have decreased levels of growth. Thus, there is no reasonable expectation that replacing the growth hormone agonist of Phares with the postulated growth hormone antagonist taught by Chen would result in inhibiting the growth of breast cancer cells.

The Answer asserts that one of ordinary skill in the art would have understood that Phares teaches that PGF reduces serum growth hormone, and that it would have been obvious to a routineer that a growth hormone antagonist would have the same effect—to block or prevent growth hormone from binding to the receptor. It is unpredictable, however, what effect that the antagonist will have at the receptor, as demonstrated by the fact that in Phares, the experimental animals treated with PGF experienced an increase in growth, whereas the instant specification teaches that animals treated with growth hormone antagonist have decreased growth. Thus, while Phares may have provided the ordinary artisan incentive to try the use of a growth hormone antagonist to reduce the growth of breast cancer cells, because of the different mechanisms and the different receptors that may be involved, the reference indeed does not provide a reasonable expectation of success of achieving the claimed result—inhibiting the growth of breast cancer cells.

CONCLUSION

For the reasons stated above, the rejections of claims 1 and 3-7 under 35 U.S.C. § 103(a) are reversed.

REVERSED

SHERMAN D. WINTERS Administrative Patent Judge	))))) BOARD OF PATENT
TONI R. SCHEINER Administrative Patent Judge	)) APPEALS AND)) INTERFERENCES
LORA M. GREEN Administrative Patent Judge	))

Appeal No. 1999-1732
Application No. 08/308,879

GATES and COOPER
HOWARD HUGHES CENTER
670 CENTER DRIVE WEST
SUITE 1050
LOS ANGELES, CA 90045

LMG/jlb